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09/692,077	10/19/2000	Kersten M. Small	13105	6315

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EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/692,077	SMALL ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,16,17,19-29,31-38 and 40-67* is/are pending in the application.

4a) Of the above claim(s) *23-29,45-62 and 64* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5, 16, 17, 19-29, 31-38, and 40-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendments and arguments set forth in the response filed 10/13/05 have been considered but are not sufficient to place the claims in condition for allowance. Applicant's remarks are addressed throughout the office action, as appropriate. Claims 1-5, 16-17, 19-29, 31, 32-38, and 40-67 are pending. Claims 23-29 and claims 45-62 and 64 are withdrawn from prosecution as being drawn to non-elected subject matter. THIS ACTION IS FINAL.

Specification

2. The amendment filed 10/13/05 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The amendment of the specification to add the reference to GenBank Accession Number #AF316895 to the specification is new matter. In the remarks, applicant indicated that this was to correct a "typographical" error. However, the replacement of #AF009500 with #AF316895 is not the correction of an obvious error. Though it was clear from the disclosure that the original reference was not correct, the correction itself was not clear from the specification as filed. Further, the publication date on the corrected GenBank accession number is a post-filing date, and the specification teaches that the record being referred to provides the longer (undeleted) receptor gene (the wild type, see p. 14), and the newly cited record provides the deletion allele.

Applicant is required to cancel the new matter in the reply to this Office Action.

3. The corrections to the sequence listing have been entered and now the sequence listing is consistent with the teachings of the specification.

Claim Objections

4. Claim 67 is objected to because of the following informalities: the word "phosphorylation" is misspelled. Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. Claim 19 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 19 is indefinite because it is not clear how hybridization with one of the sequences listed in claim 16 can be used for a "specific hybridization" that results in identifying the alleles of the polymorphism by one of the methods recited in claim 19 since none of the oligonucleotides recited in claim 19 overlap with the polymorphic position. Clarification is requested.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 31, 33-38, and 40-44 are rejected under 35 U.S.C. 102(b) as being anticipated by Heinonen (The Journal of Clinical Endocrinology & Metabolism, July 1999, as cited in the IDS).

Heinonen et al. teach a deletion of nine nucleotides in frame of the alpha-2B-adrenergic receptor molecule that results in the loss of three glutamatic acid residues from the encoded polypeptide (see Figure 1 of Heinonen et al.). The sequence deleted is identical to instant SEQ ID NO: 3. Further, the instant specification teaches that the deletion taught in this reference is identical to the deletion identified in this application (see p. 58, line 10). Heinonen et al. teach that the deletion polymorphism is associated with reduced BMR in obese, non-diabetic Finns (p. 2431). Heinonen et al. suggest a possible mechanistic explanation for the association is related to possible incapability of the encoded deletion polypeptide of being phosphorylated and desensitized in the normal manner (p. 2431, final ¶).

With regard to claim 31, Heinonen et al. teach a method of identifying an individual increased risk for developing a disease associated with alpha-2B-adrenergic receptor molecule comprising:

a. obtaining a sample having a polynucleotide encoding an alpha-2B-adrenergic receptor molecule comprising SEQ ID NO: 1 or SEQ ID NO: 2 or a fragment or a complement of the polynucleotide from the individual (p. 2430); and

b. detecting in the sample a polymorphism at a polymorphic site comprising at least one of positions 901 to 909 of SEQ ID NO: 1 or SEQ ID NO: 2 or a complement thereof, wherein the polymorphism correlates to the disease (p. 2430), thereby identifying the individual at risk for the disease. Namely, Heinonen et al. teach that alleles of the polymorphism are associated with reduced basal metabolic rate in obese subjects, and by extension that the alleles are a predictor of an increased risk of developing obesity (abstract and throughout, especially p. 2432). Heinonen

et al. teach determining a predisposition to obesity, which by extension suggests an increased likelihood of a wide variety of cardiovascular diseases that are related to obesity.

With regard to claim 38, Heinonen et al. teach a method which comprises the steps of:

a. obtaining a sample having a polynucleotide encoding an alpha-2B-adrenergic receptor molecule comprising SEQ ID NO: 1 or SEQ ID NO: 2 or a fragment or a complement of the polynucleotide from the individual (p. 2430); and

b. detecting in the sample a polymorphism at a polymorphic site comprising at least one of positions 901 to 909 of SEQ ID NO: 1 or SEQ ID NO: 2 or a complement thereof, wherein the polymorphism correlates to the disease (p. 2430). Namely, Heinonen et al. teach that alleles of the polymorphism are associated with reduced basal metabolic rate in obese subjects, and by extension that the alleles are a predictor of an increased risk of developing obesity (abstract and throughout, especially p. 2432). With regard to the language of the preamble, reciting "a method for diagnosing or prognosing an individual with a disease associated with an alpha-2B-adrenergic receptor molecule," Heinonen et al. are considered to inherently meet this step as they meet all of the structural limitations of the claim as recited.

With regard to claims 33, and 40 both versions of the alpha-2B-adrenergic receptor sequence contain both SEQ ID NO: 3 and SEQ ID NO: 4, see Figure 1.

With regard to claims 34, and 41, Heinonen et al. teach an insertion of 9 nucleotides in the long form relative to the short form.

With regard to claims 35 and 42, Heinonen et al. teach a deletion of 9 nucleotides in the short form relative to the long form.

With regard to claims 36, and 43, the complement of the polymorphism (i.e. the deleted portion) is 5'-ctcctcttc-3'.

With regard to claim 37 and 44,the alpha-2B-adrenergic receptor molecule inherently comprises SEQ ID NO: 7 or SEQ ID NO: 8, as well as "a fragment thereof" which can be as few as a single amino acid. All polypeptide sequences comprise a fragment of SEQ ID NO: 7 or SEQ ID NO: 8 given the plain language of the claim.

8. Claims 1-5, 63 and 65-67 are rejected under 35 U.S.C. 102(b) as being anticipated by Jewell-Motz (Biochemistry, 1995, Vol. 34, pages 11946-11953, as cited in the IDS).

Jewell-Motz et al. used site-directed mutagenesis to delete or substitute a 16 amino acid stretch of glutamic acid residues from the alpha-2B-adrenergic receptor molecule (see Figure 1 of Jewell-Motz et al.). The sequence deleted inherently would include instant SEQ ID NO: 3 which encodes three glutamic acid residues within a 16 amino acid repeat sequence of glutamic acids in the alpha-2B-adrenergic receptor molecule. Jewell-Motz et al. teach that the deletion of and substitution of this section results in receptors that undergo agonist-promoted phosphorylation at levels of only about 44 and 50%, respectively, relative to wild type. Jewell-Motz et al. teach that after the site-directed mutagenesis of the nucleic acid encoding the wild-type alpha-2B-adrenergic receptor molecule, presence of the mutations were detected using nucleotide tracking and sequencing. Further, they teach that final constructs were analyzed using restriction analysis and sequencing to confirm the presence of the desired mutation.

Thus, with regard to claim 1, Jewell-Motz et al. teach a method comprising:

a. obtaining a sample of a polynucleotide encoding alpha-2B-adrenergic receptor molecule comprising SEQ ID NO: 1 or SEQ ID NO: 2 or a fragment or a complement of the polynucleotide (p. 11947);

b. detecting in the sample a polymorphism at a polymorphic site located at positions 901-909 of SEQ ID NO: 1 or SEQ ID NO: 2 or a complement thereof (p. 11947) and

c. correlating the polymorphism to an alpha-2B-adrenergic receptor function (p. 1149, 2nd col. and following).

Jewell Motz et al. detect a polymorphism located at positions 901-909 of SEQ ID NO: 1 or SEQ ID NO: 2 or a complement thereof when they detect either a deletion or substitution of these nucleotides using restriction analysis and sequencing to confirm the presence of the desired mutant. It is acknoweledged that Jewell-Motz et al. also detect additional mutated positions, but the claim is broadly drawn using "comprising" language and does not exclude the detection of additional polymorphic or deleted positions. The teachings of Jewell-Motz et al. provide the manipulative method steps recited in claim 1, as the mutations detected by Jewell-Motz et al. would comprise all of nucleotide positions 901-909 of SEQ ID NO: 1 and SEQ ID NO: 2, either as a deletion or as substituted nucleotides. The mutations detected by Jewell-Motz et al. include additional nucleotides relative to these positions, but the claims are drawn using broad language and encompass detection of larger "polymorphic" regions, as detected by Jewell-Motz et al. Further, Jewell-Motz et al. teach the effects of these mutations on receptor function. Furhter, Jewell-Motz et al. correlate the presence of the mutation with a loss of agonist-promoted desensitization, thus they correlated the polymorphism to function.

With regard to claim 2, the claims require only that the polymorphism comprise "a complement" of SEQ ID NO: 3 or SEQ ID NO: 4. The phrase "a complement" is interpreted to include any molecules that contain at least a single nucleotide that is "a complement" of any portion of SEQ ID NO: 3 and SEQ ID NO: 4. The substitution mutant provided by Jewell-Motz et al. encodes a segment of glutamines which are encoded by "CCA" or "CAG", which include "a complement" of SEQ ID NO: 3 since "C" is a complement of "G."

With regard to claim 3, in Jewell-Motz et al. the wild type teach an insertion of 9 nucleotides (plus additional nucleotides) relative to the deletion mutant.

With regard to claim 4, Jewell-Motz et al. teach a deletion of 9 nucleotides relative to the wild type.

With regard to claims 5, the complement of the deleted portion contains a deletion that is the complement of 5'-ctcctcttc-3'.

With regard to newly added claim 65, the function comprises mediation of receptor desensitization as measured by adenylyl cyclase activities. With regard to claims 66 and 67, Jewell-Motz et al. teach that the polymorphism correlates with less net phosphorylation compared to wild type, consistent with no detectable change in physical G-protein coupling as delineated in agonist competition studies (p. 11950, 2nd Column).

With regard to claim 63, Jewell-Motz et al. teach a method comprising:

a. obtaining a sample of a polynucleotide encoding alpha-2B-adrenergic receptor molecule comprising SEQ ID NO: 1 or SEQ ID NO: 2 or a fragment or a complement of the polynucleotide (p. 11947);

b. indirectly detecting in the sample a polymorphism at a polymorphic site comprising at least one of nucleotide positions 901-909 of SEQ ID NO: 1 or SEQ ID NO: 2 or a complement thereof (p. 11947, first column).

The preamble of claim 63 recites a method of determining alpha-2B-adrenergic receptor function by indirectly detecting a polymorphism at a polymorphic site. The teachings of Jewell-Motz et al. provide the manipulative method steps recited in claim 63. Jewell-Motz et al. "indirectly" detect the allele present at the polymorphic site via restriction digestion.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 16, 17, 20 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heinonen et al. in view of Newton ("Chapter 6: Primers," in *PCR Essential Data*, C.R. Newton, ed., John Wiley & Sons, Chichester, 1995, pages 49-56, cited in previous office action).

Heinonen et al. teach a method of genotyping a polynucleotide encoding an alpha-2B-adrenergic receptor molecule comprising: (a) obtaining a sample comprising the polynucleotide; and (b) subjecting the polynucleotide with at least one oligonucleotide having a nucleotide sequence that is complementary to a region of the polynucleotide, and which, when hybridized to the region permits the identification of nucleotides present at a polymorphic site of the polynucleotide. Heinonen et al. teach genotyping of a polymorphic site comprising an insertion or deletion of 9 nucleotides at positions 901 to 909 of SEQ ID NO: 1 or SEQ ID NO: 2 (p. 2430, 2nd col.) by amplification and subsequent electrophoresis on a hot sequencing gel to determine the allele present. Referring in particular to part (b) of the claim 16, Heinonen et al. teach subjecting a polynucleotide to an incubation with at least one oligonucleotide, the at least one oligonucleotide having a nucleotide sequence that is complementary to a region of SEQ ID NO: 1 and SEQ ID NO: 2, and when hybridized the region permits the identification of the nucleotide present at a polymorphic site of a polynucleotide (p. 2430, Sequencing and Genotyping, for example). The hybridization of the primers used by Heinonen et al. permit the identification of the polynucleotide because they are used in an assay to identify the polymorphism. Heinonen et al. permit hybridization to occur, and identify the polymorphic site to obtain the gentoype of the individual. The polymorphism detected by Heinonen et al. is an insertion or deletion of nine nucleotides at positions 901-909 of SEQ ID NO: 1 or SEQ ID NO: 2. Heinonen et al. teach the

use of a primer which significantly overlaps with instant SEQ ID NO: 19, namely nucleotides 7-21 of instant SEQ ID NO: 19 are identical to nucleotides 1-15 of the first pri-15 of the first primer mentioned by Heinonen et al. on page 2430 in the second column.

With regard to claim 17, Heinonen et al. teach multiple rounds of PCR, and thus, teach amplification prior to hybridization (i.e. amplification in a round of PCR prior to a particular hybridization of primers in a later round).

With regard to claim 20, the oligonucleotides themselves have sequences which are nucleic acid labels.

With regard to claim 21, Heinonen et al. use restriction digestion to determine the identity of the polymorphic site.

Heinonen et al. do not teach a method wherein at least one of the oligonucleotides is SEQ ID NO: 19 (or any of the other polynucleotides listed in claim 16).

Newton et al teach the design of primers for PCR, providing guidance with respect to desirable characteristics as well as properties to avoid when designing PCR primer pairs (see entire reference, particularly pages 50-51).

In view of the teachings of Heinonen et al, and given the guidance provided by Newton regarding the design of PCR primers, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Heinonen et al so as to have employed therein a variety of different primers, including a primer consisting of instant SEQ ID NO: 19. One would have been motivated to provide additional means for the amplification of the sequence surrounding the mutation taught by Heinonen et al., and would have been motivated by the teachings of Heinonen et al. to target a region of the gene that was

successfully targeted for amplification in previous assays. As Heinonen et al demonstrates that the region of their primer may be successfully targeted in PCR amplification, an ordinary artisan would have been motivated to have selected primers that hybridize specifically to this region (including a primer consisting of SEQ ID NO: 19), rather than to have experimented to identify other regions suitable for primer hybridization, for the advantages of convenience and efficiency providing additional primers for the amplification of the region containing the mutation taught by Heinonen et al. Absent a showing of unexpected results with the particular sequence of the claim, any primers targeting the region suggested by Heinonen et al and meeting the criteria of Newton would be obvious over Henionen et al and Newton. It is further noted that as SEQ ID NO: 19 meets the desired criteria disclosed by Newton for length, melting temperature, GC content, etc., an ordinary artisan would have had a reasonable expectation of success in employing this primer, as well as a variety of other primers suggested by the references, in the method of Heinonen et al.

12. Claims 19 and 21 are is rejected under 35 U.S.C. 103(a) as being unpatentable over Heinonen et al. in view of Newton et al. as discussed in the previous rejection of claims 16, 17, 20 and 22, and further in view of Snapir et al.

Heinonen et al. do not teach a method for detection of the polymorphism using one of the specific hybridization methodologies recited in claims 19 or the methodologies discussed in claim 21.

At the time the invention was made, the detection of genetic variants using any of the recited methods was routine in the art. Snapir et al. teach methods for detecting a polymorphism

within a polynucleotide encoding an alpha-2B-adrenergic receptor molecule, wherein the polymorphism results in a loss of three glutamic acids in the encoded receptor. Snapir et al. teach that the polymorphism can be detected using a variety of routine methods including allele specific amplification and single stranded conformational polymorphism analysis (¶32) and hybridization methods such as allele specific probes and northern blot assays (¶ 33). Thus, at the time the invention was made, it would have been prima facie obvious to have modified the methods taught by Heinonen et al. in view of Newton so as to have utilized the hybridization methods taught by Snapir et al. in order to have provided additional methods for the detection of the polymorphism taught by Heinonen et al.

Claim Rejections - 35 USC § 103

13. Claims 1-5, 63, and 65-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jewell-Motz et al. in view of Henionin et al.

This 103 rejection is written against a narrow interpretation of the rejected claims which would require the detection exclusively of polymorphic positions 901 to 909 of SEQ ID NO: 1 or 2 and not a polymorphic region of greater length.

Jewell-Motz et al. teach a method comprising:

a. obtaining a sample of a polynucleotide encoding alpha-2B-adrenergic receptor molecule comprising SEQ ID NO: 1 or SEQ ID NO: 2 or a fragment or a complement of the polynucleotide (p. 11947);

b. detecting in the sample a polymorphism at a polymorphic site located at positions 901-909 of SEQ ID NO: 1 or SEQ ID NO: 2 or a complement thereof (p. 11947) and

c. correlating the polymorphism to an alpha-2B-adrenergic receptor function (p. 1149, 2nd col. and following).

Jewell Motz et al. detect a polymorphism located at positions 901-909 of SEQ ID NO: 1 or SEQ ID NO: 2 or a complement thereof when they detect either a deletion or substitution of these nucleotides using restriction analysis and sequencing to confirm the presence of the desired mutant. Jewell-Motz et al. detect the polymorphism within a larger mutated region, which results in the deletion or substitution of sixteen amino acids. Further, Jewell-Motz et al. teach the effects of these mutations on receptor function, as Jewell-Motz et al. correlate the presence of the mutation with a loss of agonist-promoted desensitization, thus they correlated the polymorphism to function.

With regard to claim 2, the claims require only that the polymorphism comprise "a complement" of SEQ ID NO: 3 or SEQ ID NO: 4. The phrase "a complement" is interpreted to include any molecules that contain at least a single nucleotide that is "a complement" of any portion of SEQ ID NO: 3 and SEQ ID NO: 4. The substitution mutant provided by Jewell-Motz et al. encodes a segment of glutamines which are encoded by "CCA" or "CAG", which include "a complement" of SEQ ID NO: 3 since "C" is a complement of "G."

With regard to claim 3, in Jewell-Motz et al. the wild type teach an insertion of 9 nucleotides (plus additional nucleotides) relative to the deletion mutant.

With regard to claim 4, Jewell-Motz et al. teach a deletion of 9 nucleotides relative to the wild type.

With regard to claims 5, the complement of the deleted portion contains a deletion that is the complement of 5'-ctcctcttc-3'.

With regard to newly added claim 65, the function comprises mediation of receptor desensitization as measured by adenylyl cyclase activities. With regard to claims 66 and 67, Jewell-Motz et al. teach that the polymorphism correlates with less net phosphorylation compared to wild type, consistent with no detectable change in physical G-protein coupling as delineated in agonist competition studies (p. 11950, 2nd Column).

With regard to claim 63, Jewell-Motz et al. teach a method comprising:

a. obtaining a sample of a polynucleotide encoding alpha-2B-adrenergic receptor molecule comprising SEQ ID NO: 1 or SEQ ID NO: 2 or a fragment or a complement of the polynucleotide (p. 11947);

b. indirectly detecting in the sample a polymorphism at a polymorphic site comprising at least one of nucleotide positions 901-909 of SEQ ID NO: 1 or SEQ ID NO: 2 or a complement thereof (p. 11947, first column).

The preamble of claim 63 recites a method of determining alpha-2B-adrenergic receptor function by indirectly detecting a polymorphism at a polymorphic site. The teachings of Jewell-Motz et al. provide the manipulative method steps recited in claim 63. Jewell-Motz et al. "indirectly" detect the allele present at the polymorphic site via restriction digestion.

Jewell-Motz et al. do not teach a method wherein the polymorphic site detected is limited to nucleotides 901 to 909 of SEQ ID NO: 1 or SEQ ID NO: 2. The instant claim is also not so limited, but this rejection is written against a narrow embodiment within the scope of the claim.

Heinonen et al. teach the identification of a three-amino acid deletion in the alpha-2B-adrenergic receptor that is caused by a nine amino acid deletion in the polynucleotide encoding the receptor. Heinonen et al. suggest that this genetic variant might also have decreased

desensitation due to loss of amino acids in a region previously shown to be critical for this response.

Thus, given the teachings of Jewell-Motz et al. in view of the teachings of Heinonen et al., it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have modified the methods taught by Jewell-Motz et al. so as to have detected and tested only molecules with the polymorphic gene encoding the three amino acid deletion, and correlated this polymorphism with the receptor function. One would have been clearly motivated by the teachings of Heinonen et al. to undertake such experimentation and testing, and one would have had an expectation of success that the polymorphism would be correlated with function based on the fact that this region was previously shown to be necessary for function.

Claim Rejections - 35 USC § 112

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 31, 33-37, 38, and 40-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are all drawn to methods of identifying an individual at increased risk for developing a disease associated with an alph-2B-adrenergic receptor molecule or methods for

diagnosing or prognosing an individual with a disease associated with an alph-2B-adrenergic receptor molecule, and the methods recite the detection of a particular polymorphism within the gene encoding the receptor. The claims further recite that the disease is selected from the group consisting of cardiovascular disease, central nervous system disease, and combinations thereof. Thus, for the practice of the claimed invention, the nature of the invention requires a knowledge of at least a predictive association between the polymorphism and the recited broad classes of disease.

With regard to the disease in question, the scope of the claims is quite broad-encompassing for the independent claims any possible disease cardiovascular or central nervous system disease that would be "associated with an alph-2B-adrenergic receptor molecule." This encompasses a wide variety of possible diseases since this receptor mediates peripheral vasoconstriction in response to agonist activation.

The specification does not contain a single working example or guidance concerning which diseases are associated with which alleles of this polymorphism.

This art area is highly unpredictable as the determination of an association between a polymorphism and a disease is an empirical endeavor. Ho et al. (Am. J. Med. Genet. 1998) teach that a deletion of nine nucleotides resulting in the deletion of three glutamate amino acids in this gene is not associated with schizophrenia nor to the response to clozapine. Salonen et al. (Circulation, October 2000) teach that men homozygous for the short form of the receptor had 2.5 times the risk of acute coronary event compared with the other two genotypes, but that the polymorphism was not associated with hypertension. Thus, even in populations where the polymorphism (at least the polymorphism in the encoded polypeptide) is predictive of one

cardiovascular disease it may not be predictive of a different disease. Further, once an association between a phenotype and a polymorphism is identified, it is sometimes contradicted by other studies. Heinonen et al. (J. of Clinical Endocrinology & Metabolism, 1999) teach that subjects homozygous for the short allele had lower basal metabolic rates than those with the long allele. A later study attempted to replicate this finding but found that the short allele was associated with increased metabolic rates, showing an opposite effect in two different populations (Pollin et al. Obesity Research, October 2000). Though some of the prior art provides associations that may be predictive in some diseases in particular populations, the instant specification does not provide specific guidance or support for the detection of any of these. Given the high degree of unpredictability exemplified in the related art, the findings of one group cannot be applied generically.

The practice of the claimed invention would require extensive experimentation in order to determine which diseases are reliably associated with the disclosed polymorphism. Such study would involve the testing of many patient and control populations for the wide variety of disease that are encompassed within the claims.

Thus, having carefully considered all of these factors- given the nature of the invention, the scope of the claims, the lack of working examples or guidance in the specification, the high level of unpredictability for the related art, and the high level of experimentation necessary to practice the claimed invention, it is concluded that it would require undue experimentation to practice the claimed invention.

Response to Remarks; Withdrawn rejections

Applicant's remarks are addressed in the order that they are provided.

The application is in compliance with the sequence rules.

As discussed previously in this office action, the amendment to the specification changing the GenBank accession number introduces new matter into the specification.

All previously set forth claim objections are overcome by the amendments to the claims.

Applicant traverses the 112 1st paragraph rejection, beginning on page 16 of the response. Applicant argues that they teach that "the altered receptor signaling directly relates to certain diseases, so that the polymorphism correlates, one step removed, to those certain diseases." However, as discussed in the rejection, this single step is a significant step. The art area of this invention is a highly unpredictable area. The portions of the specification cited in the remarks are prophetic in nature regarding the association between the polymorphism and any disease. At page 10 of the specification (cited on page 17 of the remarks) "diseases" are discussed to include a wide range of cardiovascular and CNS diseases, and the specification suggests that each of these can be diagnosed or predicted using the methods of the claimed invention. However, not a single piece of evidence is provided to show that this polymorphism is associated with all of these diseases, nor is any guidance provided as to which subset the polymorphism might be relevant to. On page 18 of the response, applicant states that they "have discovered a correlation, in particular, to cardiovascular disease, central nervous disease, and combinations thereof." If such a correlation has been discovered, no evidence of such a correlation has been provided. The discovery or identification of a correlation is different from the suggestion that one may exist. Attorney arguments do not replace evidence on the record.

Applicant appears to contradict their assertion that a correlation has been "discovered" in the next paragraph of the remarks where they discuss the fact that the specification provides guidance as to how to correlate a polymorphic site with a disease. Applicant points out that the specification provides guidance on how to accomplish the correlation of a disease with a polymorphism. However, as mentioned in the rejection, the scope of the claims is quite broad with regard to the types and etiology of diseases that applicant suggests can be correlated with the polymorphism, and this art area is highly unpredictable. For each disease it would require a separate analysis to establish a predictive relationship between the polymorphism and the disease. As discussed in the rejection, this is a highly unpredictable endeavor. Applicant states that the relevant correlation is determined statistically, not empirically. However, this statistical determination must be made based on empirical data collected from populations of patients. Though the molecular biology aspect of the invention (i.e. the actual genotyping) is routine and reasonably predictable, whether or not an association exists between a particular disease and the genotypes is highly unpredictable. The presupposition in the claims that the polymorphism is associated with any disease in particular or all cardiovascular and nervous system diseases is not supported by evidence on the record, and thus further, undue experimentation would be required to establish that such correlations exist in order to practice the claimed invention. Such experimentation is itself inventive an thus the rejection is maintained.

The previously set forth rejections under 112 2nd paragraph are withdrawn in view of the amendments to the claims.

The rejection in view Heinonen et al. is withdrawn with respect to pending claims 1-5 and 63 in view of the amendments to the claims. The rejection under Heinonen et al. is

maintained for claims 31, 33-38, and 40-44. Applicant traverses the rejection of claims 31 and 38 beginning on page 29 of the response. Applicant argues that it is an unreasonable stretch for the Examiner to equate a phenotypic variance of BMR of 100 calories per day as in any way equivalent to obesity, or even one step further removed, to cardiovascular disease. However, this is not persuasive. It was not the examiner who taught that "the identified receptor polymorphism is clearly only a risk factor or codeterminant of clinical obesity," it was Heinonen et al. The instant claims set forth a method for predicting a disease or identifying an individual at risk for a disease. Heinonen et al. teach a method for genotyping a polymorphism that is, in their words, a risk factor or codeterminant of obesity, which is clearly a known predictor or risk factor of cardiovascular disease.

The rejection under Jewell-Motz et al. is maintained for claims 1-5, and 63. Applicant traverses the rejection beginning on page 33 of the response. Applicant argues that the references does nto anticipate the claimed invention because it discloses the detection of a larger polymorphism that includes "superfluous" portions. This is not persuasive because the claims are broadly drawn to include the detection of polymorphic positions in addition to those located "at positions 901-909 of SEQ ID NO: 1 or 2." Applicant further argues that the reference does nto teach methods by detecting the polymorphism in a polynucleotide encoding the alpha 2-BAR receptor molecule. However, this is not persuasive, because as discussed by Jewell-Motz et al., the nucleic acids themselves were sequenced and tested by restriction analysis to genotype the mutations (p. 11947, Col. 1). Jewell-Motz et al. complete all of the method steps of the claimed invention. Therefore the rejection is maintained.

The remaining rejections are withdrawn in view of the amendments to the claims.

16. No claim is allowed.

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday through Wednesday, from 9:00 AM until 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones can be reached by calling (571) 272-0745.

The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306. Any inquiry of a general nature or relating to the status of this

application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Juliet C. Switzer
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Art Unit 1634

January 3, 2006